

REMARKS/ARGUMENTS

The foregoing amendments in the specification and claims are of a formal nature, and do not add new matter.

Prior to the present amendment, Claims 28-47 were pending in this application and were rejected on various grounds. With this amendment, Claims 28-32, 36-37 and 41-43 have been canceled without prejudice, Claims 33-35, 38-39 and 44 have been amended, and new Claims 48-54 have been added.

Claims 33-35, 38-40 and 44-54 are pending after entry of the instant amendment. Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional or continuation-in-part applications.

The amendments to the specification and claims are fully supported by the specification and claims as originally filed and do not constitute new matter. In addition, new Claims 48-54 are fully supported by the specification as originally filed. Support for new Claims 48-54 can be found at least on page 229, lines 30-36, on page 282, lines 12-19 and on page 308, line 38 to page 309, line 7 of the specification.

Applicants thank the Examiner for entering the amendments of September 9, 2002, and the Information Disclosure Statement of September 17, 2002.

Specification

In response to the Examiner's request, the specification has been amended to remove embedded hyperlink and/or other form of browser-executable code.

Applicants respectfully submit that all references to page and line numbers made throughout this response will be based on the present application's specification as filed, an electronic copy of which is available from the PTO website.

Priority Determination

The Examiner states that the effective filing date for the application is October 7, 1998, the filing date of 60/103,314.

As discussed below, Applicants rely on the gene amplification assay (Example 143) for patentable utility which was first disclosed in U.S. Provisional Application No. 60/162,506, filed

October 29, 1999, priority to which has been claimed in this application. Accordingly, the present application is entitled to at least the October 29, 1999 priority for subject matter defined in Claims 28-35, 38-40, and 44-54. In support, Applicants enclose herewith pages 128-162, describing the gene amplification assay (Example 20), of the U.S. Provisional Application No. 60/162,506.

Claim Rejections – 35 U.S.C. §101 and §112, First Paragraph

Claims 28-47 are rejected under 35 U.S.C. §101, allegedly “because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.” The Examiner asserts that “the specification does not disclose a function for the nucleotide of SEQ ID NO:337, encoding the polypeptide of SEQ ID NO:338, in the context of the cell or organism.” The Examiner further alleges that “a slight increase in clone copies in several types of tumors is not indicative of a specific or substantial utility for PRO1555 for use as an agent to detect or treat cancer.”

Claims 28-47 are also rejected under 35 USC §112, first paragraph, allegedly “since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility ..., one skilled in the art would not know how to use the claimed invention.” Applicants respectfully disagree with and traverse the rejections.

The Examiner alleges that the specification asserts the following nine utilities for the claimed polynucleotides and polypeptides encoded by the claimed polynucleotides:

- 1) To make hybridization probes to detect the polypeptide of SEQ ID NO: 337
- 2) To produce the PRO1555 polypeptide and fragments
- 3) For use in chromosome mapping
- 4) For use in the construction of “knock-in” or “knock-out” organisms.
- 5) For making antisense oligonucleotides
- 6) In assays to screen for compounds capable of modifying the interaction between receptor and ligand.
- 7) To make antibodies to the polypeptide encoded by the polynucleotide of SEQ ID NO: 337.

- 8) In tissue typing
- 9) To treat cancer.

See pages 4-8 of the instant Office Action.

Applicants note that portions of the instant Office Action discuss the alleged lack of utility for the PRO1555 polypeptide and the antibodies. (For example, see pages 5-6). Applicants respectfully submit that present application is directed to nucleic acids. Nevertheless, Applicants maintain that the utility is provided for the polypeptides and antibodies in the present application.

Applicants submit that the cancellation of Claims 28-32, 36-37 and 41-43 renders the rejection of these claims moot. Claims 33-35, 38-40 and 44-54 have patentable utility for the reasons discussed below.

Legal Standard

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). See, also *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is *a preponderance of the totality of the evidence* under consideration. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that *it is more likely than not* that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, shifts the burden of rebuttal to the applicant. The issue will then be decided on the totality of evidence.

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient*, at least with regard to defining a "substantial" utility." M.P.E.P. 2107.01, emphasis added. Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, the Utility Guidelines restate the Patent Office's long established position that any asserted utility has to be "credible." "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record . . . that is probative of the applicant's assertions." M.P.E.P. 2107 II(B)(1)(ii). Such standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion.

Proper Application of the Legal Standard

Applicants submit that the invention defined by the presently amended claims has specific, substantial and credible utility for the nucleic acids encoding the PRO1555 polypeptide.

As discussed above, Applicants rely on the gene amplification data for priority and to establish patentable utility for nucleic acids encoding the PRO1555 polypeptide. This data was first disclosed in Provisional Application No. 60/162,506 filed on October 29, 1999, the priority of which is claimed in the present application. Hence, the effective filing date of the present application is October 29, 1999 for subject matter defined in Claims 33-35, 38-40, and 44-54.

Gene amplification is an essential mechanism for oncogene activation. The gene amplification assay is well-described in Example 143 of the present application, the inventors isolated genomic DNA from a variety of primary cancers and cancer cell lines that are listed in Table 8, including primary lung and colon tumors of the type and stage indicated in Table 7. As a negative control, DNA was isolated from the cells of ten normal healthy individuals, which was pooled and used as a control. Gene amplification was monitored using real-time quantitative TaqMan PCR. Table 8 shows the resulting gene amplification data. Further, Example 143 explains that the results of TaqMan™ PCR are reported in ΔC_t units, wherein one unit corresponds to one PCR cycle or approximately a 2-fold amplification relative to control, two units correspond to 4-fold amplification, 3 units to 8-fold amplification etc. The specification discloses that the nucleic acids encoding PRO1555 had ΔC_t value of > 1.0 , which is **more than 2-fold increase**, for (1) in primary lung tumors: LT13, LT15, LT16, HF-000631, HF-000840, and HF-000842; (2) in lung cell lines: A549, Calu-1, Calu-6, H441, H460, and SKMES1; (3) in primary colon tumors: CT15, CT16, CT17, and colon tumor centers HF-000539 and HF-000575; (4) in colon cell lines: SW620, Colo320 and HCT116; (5) in breast tumor center HF-000545; (6) in kidney tumor center HF-000611; and (7) in testis tumor margin HF-000716 and testis tumor center HF-000733. Because amplification of DNA73744-1665 occurs in various tumors, it is highly probable to play a significant role in tumor formation or growth. (See page 503 lines 21-33).

It is well known that gene amplification occurs in most solid tumors, and generally is associated with poor prognosis.

In support, Applicants submit a Declaration by Dr. Audrey Goddard with this response and particularly draw the Examiner's attention to page 3 of the declaration which clearly states that:

It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.*, non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy. (Emphasis added).

The attached Declaration by Audrey Goddard clearly establishes that the TaqMan real-time PCR method described in Example 143 has gained wide recognition for its versatility, sensitivity and accuracy, and is in extensive use for the study of gene amplification. The facts disclosed in the Declaration also confirm that based upon the gene amplification results, one of ordinary skill would find it credible that polynucleotide of SEQ ID NO: 337 encoding the PRO1555 polypeptide is a diagnostic marker of human lung, colon, breast, kidney, and testis cancer.

Accordingly, the claimed invention has a specific, substantial and well established utility that is well described in the specification.

Applicants respectfully submit that based on the teachings of Example 143 and the general knowledge available in the art at the priority date of the invention, one skilled in the art would be able to practice the claimed invention in its full scope without any undue experimentation. As the M.P.E.P. states, "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation" *In re Certain Limited-charge cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983),

aff. sub nom., Massachusetts Institute of Technology v A.B. Fortia, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985) M.P.E.P. 2164.01.

Furthermore, based on the instant disclosure and the advanced knowledge in the art at the time of filing, one skilled in the art would know exactly how to make and use these nucleic acids for the diagnosis of lung, breast, colon, kidney, and testis tumors; for example, by using diagnostic methods based on hybridization to such amplified sequences.

In view of the above, Applicants respectfully request the Examiner to reconsider and withdraw the rejection of under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph.

Claim Rejection Under 35 U.S.C. §112, First Paragraph (Written Description)

Claims 28-47 are rejected under 35 U.S.C. §112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention." The Examiner specifically asserts that "the specification does not teach functional or structural characteristics of all claimed polynucleotides. The description of one polynucleotide encoding a PRO polypeptide (SEQ ID NO: 338) is not adequate written description of an entire genus of functionally equivalent polynucleotides and polypeptides." Applicants respectfully disagree and traverse this rejection to the pending claims.

Applicants submit that the cancellation of Claims 28-32, 36-37 and 41-43, and amendment to Claim 44 (and, as a consequence, those claims dependent from the same) renders the rejection of these claims moot.

The Examiner is therefore respectfully requested to reconsider and withdraw the rejection of these claims for allegedly lacking written support.

Deposit Requirement

The Examiner states that the specification indicates that a deposit of the nucleic acid molecules was made under the Budapest Treaty, but Applicants have failed to provide a copy of the deposit receipt. In response, Applicants enclose herewith a copy of the deposit receipt indicating that DNA73744-1665 deposit, ATCC Deposit No. 203322, was made by Applicants on October 6, 1998.

The Examiner also alleges that the address for the depository, for example on paragraph 4396 of the specification, is missing. Applicants respectfully submit that Applicants cannot find the location in paragraph 4396 or in any of the adjacent paragraphs wherein the depository address is missing as indicated by the Examiner. However, Applicants respectfully point the Examiner to page 517, line 1 of the specification wherein the specification clearly discloses that the deposit was made under the Budapest Treaty. Applicants submit that the specification correctly provides the accession number for the deposit, the date of the deposit, the description of the deposited material, and the name and *address* of the depository. See starting on paragraph page 517, line 1 of the specification.

Applicants further submit that the specification has been amended to incorporate the requisite assurances that the deposit will be maintained "for 30 years from the date of deposit and for at least five (5) years after the most recent request for the furnishing of a sample of the deposit received by the depository" and to recite that "all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of the pertinent U.S. patent."

Accordingly, Applicants believe that the present rejection should be withdrawn.

Claims 28-32, 36-37 and 41-42 has been cancelled without prejudice and hence, the rejection to these claim is believed to be moot, and should be withdrawn.

Claim Rejections – 35 U.S.C. § 112, Second Paragraph

Claims 28-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner alleges that Claims 28-47 are rendered indefinite because of the phrase "extracellular domain". The Examiner also alleges that Claims 42 and 43 are rendered indefinite because of the phrase "stringent conditions".

Since the terms "the extracellular domain" and "extracellular domain ... lacking its associated signal peptide" are no longer present in Claims 33 (and, as a consequence, those claims dependent from the same), the rejection is believed to be moot, and should be withdrawn.

Claims 28-32, 36-37 and 41-43 have been cancelled without prejudice and hence, the

rejection to these claims is believed to be moot, and should be withdrawn.

Claim Rejections - 35 U.S.C. §102(b)

Claims 41-43 are rejected under 35 U.S.C. §102(b) as being anticipated by Inoue, *et al.*, (Accession No. AB03083, dated 2000). Claim 43 is also rejected under 35 U.S.C. §102(b) as being anticipated by Doh-ura, K, *et al.*, (Accession No. AF051726, dated 1999).

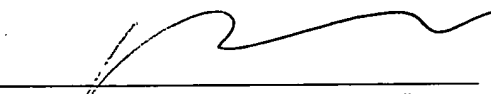
Claims 41-43 have been canceled. Accordingly, the rejection to these claims is believed to be moot and should be withdrawn.

CONCLUSION

In conclusion, the present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned attorney at the telephone number shown below. Please charge any additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2830 P1C63**). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: September 16, 2004

By: 
Panpan Gao (Reg. No. 43,626)

HELLER EHRMAN WHITE & McAULIFFE LLP
275 Middlefield Road
Menlo Park, California 94025-3506
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

SV 2061607 v1
9/16/04 2:57 PM (39780.2830)